

A Prospective Study of Mortality of Several Occupational Groups

Special Emphasis on Lung Cancer

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The study was primarily concerned with the risk of lung cancer in certain occupations. One occupation, asbestos workers, was found to have a definite increased risk of lung cancer, and the risk increased with length of time in the occupation. No other occupation was found to have increased lung cancer hazard. Other causes of mortality were not found related to these occupations except for two groups that had excess mortality from both cancers of the mouth, pharynx, and larynx and from cirrhosis of the liver. These diseases are associated with alcohol consumption, and this is the most likely explanation. The problems involved in the case control and prospective study sequence are discussed. Also the possible masking effect of such a powerful etiologic factor as cigarette smoking is discussed.

A PROSPECTIVE study of many occupations suspected of having increased risk of lung cancer was initiated in 1954. Suspicion had been aroused by an earlier case-control study.¹ Several interim reports have been made,^{2,3} and this is the final report.

Method

The goal of population size for each occupational group was 6,000 men, each to be followed for at least five years. These conditions were set to assure a 95% probability of identifying any study occupation which carried an increased risk for lung cancer of twofold or greater.

The only readily accessible source for populations of this size within a single occupation was union organizations which were cooperative in furnishing membership mailing lists and in co-sponsoring the appeal for participation by

their members. Data were collected with a one-page questionnaire and a succession of three mailings at monthly intervals in the years 1954 to 1957. An 85% response rate was achieved.

Some populations of interest could not be found in sufficient numbers (electric bridge crane operators and marine engineers and firemen). Other occupational groups were followed because they were by-products of collecting suspect occupations (sheet metal workers, not welding, and plumbers not exposed to asbestos), suspect because of a study by others (printers),⁴ and a nonsuspect control population (public utility employees).

The questionnaires asked the respondent to specify his occupational title and indicate the years spent in this occupation. Specific information was asked about exposures known to be frequently associated with certain occupations. For example, plumbers, steam fitters, and boilermakers were asked if they worked with asbestos insulation. Welders were asked to identify the types of metals usually worked on, kinds of welding rods, and working conditions. In addition to occupational information, the questionnaire asked about cigarette smoking, daily consumption, and years of smoking.

Calculation of person-years at risk was accomplished by a computer program which automatically aged each man and assigned each month of his risk exposure to the appropriate age group until such time as that individual's follow-up ended. In the earlier reports,^{2,3} follow-up was terminated either by the subject's death or by the end of the study period. An age ceiling of 69 years was used in the present report. Thus, a subject was followed until one of three conditions were met, (1) death; (2) his 70th birthday; or (3) the date for the end of the study (Dec 31, 1962).

Follow-up consisted of identifying deaths and determining causes of mortality. This was done by checking all adult male deaths in California during 1954 to 1962 against name listings of the study populations. Search was made by clerical identification through 1959 and by automated equipment through 1962.

A total of 121,314 questionnaires were collected. Study groups were limited to male re-

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Table 1.—Observed and Expected Deaths From Lung Cancer*

Occupational Group	Person-Years of Observation Ages 35 to 69	Observed Deaths	Expected Deaths†
Welders and burners	81,389	49	46.50
Sheetmetal workers (not welding)	23,008	10	15.75
Public utility employees	66,013	46	50.11
Public utility employees in suspect job classifications	10,733	6	7.22
Marine engineers and firemen	10,722	11	10.19
Electric bridge crane operators	2,274	1	1.61
Painters and decorators	84,263	90	76.30
Asbestos workers	3,830	10	3.02‡
Plumbers (asbestos exposed)	16,816	16	13.15
Plumbers (no asbestos)	54,815	33	42.22
Boilermakers (asbestos exposed)	32,150	25	27.75
Cooks	42,324	37	33.79
Culinary workers (never cooks)	19,533	21	14.40
Printers	34,788	13	26.00‡

*Fourteen occupational groups, follow-up period through December 1962.

†Expected deaths are based on age and smoking specific rates for the total study population.

‡Observed-expected difference significant at the 0.05 level as tested by chi-square.

spondents age 35 through 64 at the time of completing the questionnaire. The study population totaled 68,153 men. The study period provided 482,658 person-years of observation and 4,706 deaths within the study population.

Data analysis has been carried out by internal comparisons using the mortality experience of the total group as a base of reference. Previous analyses using general population mortality³ indicated a deficit of deaths from lethal diseases with prolonged disabling morbidity as might be expected in a largely working population. Significant deviations from expected lung cancer mortality were limited to two occupational groups in a previous analysis,³ with these deviations in opposite directions, so that the whole population seemed a reasonable base of reference.

Lung Cancer Results

The major theme of this project has been the investigation of lung cancer death rates and their relationship to certain occupational exposures. Each of the 14 occupations studied were first examined by comparing the observed number of lung cancer deaths with the expected number calculated with rates, specific for age and smoking amount, observed for all occupational groups combined. In addition, age-smoking specific rates standardized by the direct method were calculated within each occupation to determine the effect on mortality of lengths of exposure to the occupation.

In Table 1 the expected number of deaths for each occupation was calculated using lung cancer death rates for the total group by five-year age-group categories covering the span from 35 to 69, and the smoking categories of nonsmokers, less than one pack a day, about one pack a day, more than one pack a day, and unknown smoking status. These rates, applied to the age-smoking-specific person-years for a particular occupation, led to the expected number of deaths from lung cancer in that occupation. Since each occupation contributes to the total population rate, the deviation of an occupation rate from the standard is a conservative figure. The difference between this expected number and the observed number was tested for significance by the chi-square statistic calculated in a manner similar to that presented by Mantel.⁵ Only two occupations showed a lung cancer rate significantly different from that of the total study population. Asbestos workers had a significant excess, while printers had a significant deficit. Each of these occupations will be discussed separately.

The last method of examining these occupations and their relation to lung cancer was to calculate for each occupation a gradient of age-smoking standardized rates by length of time spent in the occupation. The person-years of observation and the lung cancer deaths were assigned to exposure time

Table 2.—*Asbestos Workers' Risk for Lung Cancer**

Occupation	Length of Time in Occupation (yr)		
	1-11	12-22	23-33
Asbestos workers	1.4	2.5	4.7
All other occupations	1.00	1.00	1.00

*Determined by length of time in the occupation relative to the risk for all other occupational groups.

groups depending on number of years of reported employment in the occupation; 1 to 11 years, 12 to 22 years, 23 to 33 years, and 34 or more years. This breakdown was an addition to the age and smoking group assignments already made, and standardized rates were then calculated for the four exposure periods for each of the 14 occupations. The direct method of standardization was applied using a hypothetical rectangular population distribution. Observed age-smoking-specific rates were summed for all seven age groups and five smoking classes for each of the four occupational time periods. The resulting number was divided by the total of 35 categories. In effect, standardization was to a hypothetical population composed of equal numbers in all 35 age-smoking-time in occupation groups. As is always true in standardization, the result is a figure created for comparison only and has no meaning or function apart from that of comparison with another similarly derived figure. The reader is cautioned about comparing any rates reported here to rates from other sources. We have refrained wherever possible from reporting absolute values for this essentially useless information.

In each occupation the shortest exposure period (1 to 11) had its rate set to 1.00, and the remaining three exposure groups were examined in relation to the experience of the minimally exposed group. No gradient was observed for any of the occupations except the asbestos workers, and, since they are dealt with later, no table is presented.

Printers.—The significant deficit of lung cancer deaths among workers in the various trades of the printing industry were reported in an earlier paper based on the same data.³ Examination of occupational and exposure subgroups within the printing trade, group failed to suggest systematic grounds for the observed deficiency. We balked then, as now, at assuming the existence of some

Table 3.—*Number of Deaths From Indicated Specific Causes Used in Occupational Analysis*

Cause of Death	ICD Code	Total Deaths
Cancer of mouth, larynx, & pharynx	141, 143-148, 161	43
Esophagus	150	32
Stomach	151	109
Pancreas	157	71
Bladder	181	27
Emphysema	502.0, 527.1	58
Lymphosarcoma, leukemia	200.204	57
Coronary heart disease	420	1,718
Hypertensive heart disease	440-443	101
Cirrhosis of liver	581	198

unknown anticarcinogenic factor to which printers were exposed. Chance seems the more likely explanation. It was suggested that further follow-up would find the printers "catching up." Follow-up on this group has been carried through June 1965 with identification of 17 additional lung cancer deaths. Computing the additional person-years over the same time period gives a total number of expected lung cancer deaths among printers of 38.58. With an observed number of 30 deaths for this period, the deficit of about 8½ deaths is some distance from significance, so at this point (June 1965) in follow-up, we may say that the printers show no significant deficit of observed deaths.

Asbestos Workers.—There were ten deaths among asbestos workers union members due to lung cancer, well above the expected number of 3.02. The difference is significant beyond the 0.01 level.

An important area of concern in the study of asbestos inhalation and lung cancer is the effect of type, time period, and amount of asbestos exposure. One indication that an occupational exposure is "dosage-related" would be evidence of a gradient of age-smoking standardized rates by length of time in the occupation. Asbestos workers showed such a gradient. They had an adjusted rate per 100,000 person-years of 122 for those in the occupation 11 years or less, 236 for those with 12 to 22 years exposure, 378 for the group with 23 to 33 years. There were no lung cancer deaths in the small group (166 person-years) who had 34 or more years in the asbestos workers' union. If the rate of 122 found for the exposure period of 1 to 11

Table 4.—Deaths From Oral Cancer and Cirrhosis of the Liver in two Occupations

Cause of Death	Occupation	Observed	Expected*
Cancer of mouth, pharynx, 6 larynx (141, 143-148, 161)	Marine engineers and firemen	4	1.2†
	Culinary workers (never cooks)	6	1.8†
Cirrhosis of liver (581)	Marine engineers and firemen	10	4.8†
	Culinary workers (never cooks)	22	8.1†

*All expected numbers¹ are based on the age and smoking specific rates for the total study population.

†Observed-expected difference significant at the 0.05 level as tested by chi-square.

years is taken as Unity risk, the 12 to 22 years group has a relative risk of 1.9 and the 23 to 33 years group has one of 3.1.

One method used for comparing asbestos workers to other occupations was to calculate age-smoking standardized rates of lung cancer for all occupations except asbestos workers and compare, by exposure times, the increased risk for asbestos workers. The results are presented in Table 2. When the rates for all other occupations are taken as unit risk, the relative risk for asbestos workers is 1.4 at the lowest exposure time, 2.5 at the 12 to 22 years level, and 4.7 for 23 to 33 years in the occupation.

Obviously, asbestos exposure is dangerous in its relationship to lung cancer, and, in addition, the risk noticeably increases with increased time in the occupation.

Mesotheliomas have been related to asbestos in the recent literature.⁶ We found only three mesotheliomas, one in a boiler-maker, one in a sheet metal worker, and one in a marine engineer. All involved the pleura. Another occurred in an asbestos worker who died of metastatic cerebral carcinoma attributed to "carcinoma of the stomach (endothelioma)." This may be a mesothelioma, but we have been unsuccessful in obtaining further pathological information.

Death From Other Causes.—Although the primary concern of this project was lung cancer, the procedures used made it possible to examine other causes of death. Observed and expected deaths were calculated by occupation and tested for significance for any cause of death with numbers sufficiently large enough to warrant statistical analysis. The causes examined and the International Classification of Diseases codes that define them are in Table 3 along with the total number of deaths observed for each cause.

The observed and expected number of deaths for each of the ten causes and each of the 14 occupations were calculated. The observed-expected difference was then tested for significance by chi-square.⁶ The total number of tests was 140 (10 causes, 14 occupations). Seven of these 140 comparisons were significant at the 0.05 level, a result which could easily be accounted for by chance alone. One may expect that 140 independent comparisons will, due to chance variation only, result in seven statistics significant at the 0.05 level. Where there is no obvious connection between an excess number of deaths and a particular occupation, the likelihood is that chance resulted in significant difference. Four of these excesses are particularly interesting, however, because there is a possible relationship; these are presented in Table 4.

The numbers in Table 4 are small, but it is provocative that the only two occupations to show a significant excess of oral cancer are also the only two occupations to show a significant excess of deaths from cirrhosis of the liver. On the basis of the well-known relation between alcoholic intake and deaths from cirrhosis of the liver and the relation ship found between alcoholic intake and oral malignancies,⁷ it seems possible that the observed excess of oral cancer is not due either to an occupational exposure or to chance, but is the result of the covariation of an individual social behavior and occupational choice.

Comment

The prospective study of certain occupations possibly associated with lung cancer was a sequel to the pilot case-control study in which the suspect occupations were identified.¹ This sequence is the usually accept-

ed pattern for exploratory and confirmatory epidemiological studies of chronic disease related to environmental factors. The study of lung cancer and cigarette smoking is a classic example of the successful application of this pattern. Such studies require many years of data collection, much of it waiting first for cases to appear for case-control comparisons and then for accumulation of mortality experience by the prospective study groups. In view of the time involved in such studies, it should be profitable to consider the problems and pitfalls of the present studies and the limitations of this epidemiological technique for identifying and proving exogenous carcinogens.

The initial case-control study¹ was a logical and reasonable attempt to identify suspect occupational exposures associated with lung cancer occurrence. Difficulties arose, however, in data analysis for a number of reasons, (1) multiple occupational experiences by individuals, (2) lack of information as to which and how much of several possible inhalation exposures in a particular occupation had been experienced by an individual, (3) the relationship in time of a particular occupational exposure and onset of disease, and (4) lack of objective means of distinguishing real from chance associations while viewing many variables in the contrast populations.

The case-control study identified seven occupational groups in which there were two or more times as many cases as controls. In only one occupation—welders—were the numbers adequate to reach statistical significance; in another—asbestos workers—numbers were of borderline significance. The other five occupations were considered worthy of further study based on excess lung cancer cases and a reasonable suspicion of the inhalation exposures involved. A means for collecting populations of six of these was developed from union organizations. Smelter workers were not included in this study because of inaccessibility of a sizeable population.

The choice of suspect occupations, then, was not anchored wholly in firm statistical probabilities but was based on statistical possibilities and intuitive rationale. The choices available for further investigation were to repeat the case-control study in the hope that those occupations found at high

risk in the initial study would again be so identified or to undertake a prospective study of each high risk suspect occupation. The latter course was chosen as the more definitive. This was dictated partly by the disease under study. The high incidence of lung cancer brings the population size required for prospective study within reasonable limits. Also, lung cancer is not ordinarily preceded by a prolonged incapacitating period of development. The clinical disease is usually rapidly fatal once it is manifest. This removes many problems involved in a disease which is more disabling, less lethal, and which would provide fewer cases as a cause of death in a working population being observed prospectively.

The prospective study produced only one occupational exposure associated with a significant excess of lung cancer—asbestos workers. The original case-control study found such exposure occurring in excess among lung cancer cases at the borderline of statistical significance. Welders appeared in statistically significant excess numbers in the case-control study but failed to show a significant excess risk in the prospective study. This raises the question as to whether in the case-control study asbestos exposure was responsible for the only “real” excess and the other occupations with excesses represent “chance” findings that are inevitable when many independent variables are being examined in the same two populations.

From what is already known of asbestos exposure it would be surprising if one failed to find an excess of lung cancer among workers with a prolonged period of occupational exposure. In the prospective study an attempt was made to assemble populations of 5,000 or more men in the specific occupational exposures being studied. For asbestos exposure this involved including plumbers and boilermakers who handled some asbestos in their work. A significant excess of lung cancer did not appear in this total population, and only when a small subgroup with known heavy exposure was examined separately did the increased risk appear. This group accounted for only 7% of the person-years of follow-up but for almost one fifth of the lung cancer deaths among workers with asbestos exposure.

This raises the question whether there

might not be other occupational subgroup who have heavier exposure to carcinogenic substances that have been diluted out by the larger proportion within the occupation who have lesser exposure to such substances. This could be the case, but it would be difficult to search for such exposure without some suspicion founded on other evidence as to what the substance might be. Blind searching among multiple factors leads to chance excesses that settle nothing and may send one on a will-o'-the-wisp pursuit.

Cigarette smoking as an extremely important variable in lung cancer causation complicates the search for other causes. Data on this variable collected in the earlier case-control study, along with the occupational history, provided an early report showing the importance of cigarette smoking in causing lung cancer.⁴ Whether another pulmonary carcinogen with cigarette smoking will be independent, additive, synergistic, or multiplicative is a crucial question. In the former circumstance cigarette smoking could obliterate an important factor that would be maximally evident in the small proportion of the population who do not smoke. In the latter circumstance, however, cigarette smoking would not mask and might amplify the effect of a second agent. The lung cancer experience of heavy cigarette smokers would then provide guidance in a search for such additional carcinogenic exposures. Our experience in this study and with other prospective data has favored the additive rather than the multiplicative relationship in the interaction of cigarette smoking and other carcinogenic factors in lung cancer occurrence,^{3,8,9} although others have favored the latter concept.^{10,11} None of the heavy cigarette smoking components of the occupational groups in this study have shown an excess that might signal an underlying synergism. Since no occupational group had more than two lung cancer deaths among nonsmokers there are inadequate data to suggest a carcinogenic factor independent of smoking with the possible exception of the small group with excessive asbestos exposure in which one lung cancer death occurred in a noncigarette smoker and none was expected.

Summary

A prospective study of mortality was carried out among 68,153 men, 35 to 64 years of age, subdivided into 14 occupational groups, and followed up, on the average, a little over seven years. The principal interest of the study was lung cancer risk associated with certain occupations. Only one group—men belonging to asbestos workers unions—had a significant excess of lung cancer. The increased lung cancer risk was related to number of years spent in the occupation. Another occupational group—printers—who in the early years of the study had a significant deficit of lung cancer no longer do; most of the deficit was eventually made up.

Other causes of mortality bore no discernible relationship to the studied occupations. Two occupational groups had both an excess of deaths from cirrhosis of the liver and oral cancer. Both these diseases have been related to alcohol consumption, and this is a more likely explanation than any thing else associated with these occupations.

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